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Effect Of Clonidine On The Target Dose Of Propofol: Bispectral Index Evaluation

ORIGINAL

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Abstract

Background: The increasing evidence associating general anaesthetics with neurotoxicity and post-operative cognitive disturbances, mainly with deeper levels of anaesthetics, has led to more frequent use of adjuvants. This study aimed to analyse the effect of clonidine on the target dose of propofol in total intravenous anaesthesia.

Methods: A randomised, double-blind clinical trial was performed in a large hospital located in the southern region of Ceará, Brazil. Fifty-one patients from the anaesthesia outpatient clinic were enrolled. Patients were divided into two groups: one group received 100 mL of 0.9% sterile saline, and the other group received 100 mL of 0.9% sterile saline with clonidine at a dose of 3 µg/kg. A target-controlled infusion pump was used to administer propofol, following the modified Marsh pharmacokinetic model and aiming for a bispectral index (BIS) score of approximately 40 for intubation and 45 for anaesthesia maintenance. The anaesthesiologist was informed which group the patient belonged to after completion of surgery and data recording.

Results: The chi-squared test was used to evaluate the distribution of the samples with respect to gender, and the Student's t-test was used to evaluate the parametric variables. There was no statistically significant difference between the samples. A significant difference was observed in the target dose of propofol between the two groups during the maintenance and awakening phases, but not at the time of intubation.

Conclusions: Clonidine pre-operatively administered at a dose of 3 µg/kg significantly reduced the target dose of propofol needed to maintain adequate levels of anaesthesia as measured by BIS.

Keywords
Propofol, Clonidine, Bispectral Index, General Anaesthesia, Adjuvant

Background

Adjuvants have been used since the advent of anaesthetic use, and are gaining increasing importance in modern anaesthesia. General anaesthesia encompasses various states (hypnosis, pain elimination, inhibition of automatic reflexes, and muscular relaxation) which are impossible to achieve with a single drug. Atropine was administered prophylactically with the first inhalant anaesthetic (chloroform) to attenuate chloroform's hypersialosis effect. [1]

Although the mechanisms of action of general anaesthetics are still not completely understood, it is known that they act in various locations, with each medication acting in one specific location, [2] Currently, the most accepted theory is that anaesthetics act by stimulating [1] $GABA_A$ receptors, which inhibits NMDA receptors and blocks excitation at the cortical level. [2]

Evidence suggests that some anaesthetic drugs have a neurotoxic effect that continues beyond the exposure time, altering genes and protein expression. [3] Harmful effects have been recorded following exposure to ketamine, midazolam, propofol, isoflurane, sevoflurane, and desflurane. [3, 5] Cognitive disturbances are common, mainly in elderly patients. [4]

It is unknown whether this neurotoxic effect is related to the drug used, the dose of anaesthetic, or the depth of the anaesthesia, or whether it derives from characteristics that are inherent to the patient. However, promising strategies attribute a neuroprotective effect to lithium, melatonin, xenon, and alpha -2 (α2)–agonists. [3, 5]

Adjuvants act in an additive or synergistic manner with anaesthetics, facilitating the use of lower anaesthetic doses and minimizing their collateral effects. Adjuvants act in different, atypical locations. The majority of hypnotics produce their effects by connecting to the inhibitory gamma-aminobutyric acid A ($GABA_A$) receptor, stimulating it or blocking the excitatory effect of the N-*methyl*-D-aspartate (NMDA) receptor. [2] Alpha-2 agonists, of which clonidine was the first to be approved for use in humans, act on the descending noradrenergic path to modulate pain, as well as on the 2 *locus coeruleus*, where they have a sedative effect. When used in association with general anaesthesia, clonidine permits the use of lower hypnotic doses, and some studies have shown an enhanced pain-modulating effect when it is administered in the intrathecal space. [6]

Clonidine is an adjuvant with an anxiolytic effect similar to that produced by the benzodiazepines, [7] and it has been used to treat panic disorders. [8] It can, however, produce an anxiogenic effect in larger doses.

When used immediately before surgery, and soon after induction of anaesthesia, it has a pain-modulating and sedative effect and provides greater hemodynamic stability, effects that continue postoperatively. Clonidine reduces the doses of halogenated anaesthetics when it is adjusted by hemodynamic response. [9]

Various studies have reported on the use of clonidine as a pre-anaesthetic medication and have shown its effects on hemodynamic stability, postoperative pain, hypnosis-sparing, and nausea and vomiting reduction. [10-13] This study aimed to analyse the effect of clonidine on the target dose of propofol in total intravenous anaesthesia.

Methods

The current study were approved by the ethical committe of platform Brazil (CAAE 14626613.0.00000.0082), following the laws of the declaration of Helsincki. All patients received information and signed an informed consent.

A randomised, double-blind clinical trial was performed in a large hospital located in a municipality in the southern region of Ceará, Brazil. Patients undergoing laparoscopic cholecystectomy and oral and maxillofacial surgery were enrolled.

Sixty-five patients in the outpatient anaesthesia clinic were identified as potential candidates. After

applying inclusion criteria (>15 and <70 years of age, physical state P [American Society of Anesthesiologists, ASA] I-II, body mass index [BMI] below 35) and exclusion criteria (patients chronically taking benzodiazepines, barbiturates or opioid analgesics, drug addicts, patients with psychiatric disorders), 51 patients remained.

The patients were randomly assigned to either the clonidine or placebo group using a simple process of drawing names from envelopes. Twenty-six patients received clonidine and 25 received a saline solution.

Clonidine was prepared in 100 mL of 0.9% sterile saline (SS) at a dose of 3 µg/kg, at the surgical centre's pharmacy by the responsible pharmacist. The identification on the saline solution only included the patient's name. The group selected to receive the placebo received 100 mL of 0.9% SS without any additive, which was also dispensed by the surgical centre's pharmacy. One anaesthesiologist participated in the double-blind study; neither patients, nor the anaesthesiologist knew the identities of the groups.

All the patients received standard monitoring, which involved pulse oximetry, cardiography, non-invasive blood pressure measurement, capnography following orotracheal intubation, and assessment of temperature and hypnosis, using a unilateral 3BIS VISTA Aspect® monitor. The standard solution of 100 mL of 0.9% SS received from the pharmacy was administered intravenously over 10 min. Ten minutes after the end of the infusion, anaesthesia was induced with a fentanyl bolus at a dose of 3 µg/kg. Next, propofol fresenius® was administered through a target-controlled infusion pump (Base Primea Fresenius®), using the modified Marsh model. The initial programmed target dose was 4 µg/mL, adjusted to reach a BIS (bispectral index) score of 40. Remifentanil was initiated at a dose of 0.30 µg/kg/min, followed by 1 mg/kg of lidocaine and 0.15 mg/kg of cisatracurium.

Anaesthesia was maintained with propofol and remifentanil, aiming for a BIS score of approximately 45, and the target dose of propofol was recorded again at 30 minutes. At the conclusion of the procedure, the propofol pump was turned off, the remifentanil infusion was reduced to 0.05 µg/kg/min and the team waited for the patient to spontaneously awaken.

All patients received 4 mg ondansetron and 8 mg dexamethasone as prophylaxis for nausea and vomiting. An analgesic with a local anaesthetic was applied to the incision and 30 mg/kg dipyrone and 1.5 mg/kg ketoprofen were administered systemically, except in cases of reported allergy.

All patients were aroused with 1 mg of atropine and 50 mg/kg of neostigmine. Two patients required a supplemental dose of 0.5 mg of atropine due to severe bradycardia (<40 bpm), and recovered without further complications. Patients were sent to the post-anaesthetics recovery room and were discharged 3 to 4 h later, after having reached an Aldrete-Kroulik score of 9.

Results

The statistical analysis of group homogeneity with respect to the non-parametric distribution of variables was performed using the x^2 test, with a Yates correction, yielding $x^2=0.024$ with 1 degree of freedom and p = 0.8772, showing that there was no statistically significant difference between the samples **(Table 1)**.

Table 1. Distribution by gender of placebo and clonidine groups

Gender	Clonidine	Placebo	Total
Male	14	14	28
Female	12	11	23
Total	26	25	51

The x^2 test, with Yates correction, yielded $x^2=0.024$ with 1 degree of freedom and p = 0.8772, showing that there was no statistically significant difference in the distribution of gender between the groups.

The Student's t-test was used to evaluate the differences in means with respect to age, weight, height, and the mean target doses of propofol. There was no statistically significant difference between the samples with respect to age, weight, or height **(Tables 2** and **3)**. However, a significant difference in the target dose of propofol was observed between the 2 groups in the maintenance and awakening phases, but not at the time of intubation **(Table 4)**.

The most significant difference occurred at 30 min, where a $p < 0.0001$ was calculated with a

Table 2. Demographic distribution of the clonidine group.

Gender	Age	Weight	Height	BMI
M	50	72	1.72	24.34
M	25	74	1.73	24.73
M	37	81	1.71	27.70
M	16	49	1.72	16.66
M	27	60	1.65	22.04
M	19	65	1.70	22.49
M	39	62	1.80	19.14
M	59	62	1.60	24.22
M	15	53	1.64	19.71
M	23	54	1.62	20.58
F	54	40	1.49	18.02
F	19	56	1.54	23.61
F	41	62	1.55	25.81
F	66	56	1.51	24.56
F	38	55	1.55	22.89
M	24	70	1.75	22.86
F	43	63	1.53	26.91
F	58	75	1.55	31.22
F	20	57	1.60	22.20
M	21	67	1.68	23.74
F	22	62	1.76	20.02
M	16	60	1.67	21.51
F	63	72	1.52	31.16
F	52	67	1.54	28.25
M	18	68	1.70	23.53
F	42	57	1.65	20.94
Mean and SD	34.88 ± 16.55	62.27±8.96	1.62±0.09	23.42±3.61

M= male; F = female; BMI = body mass index; SD = standard deviation

Table 3. Demographic distribution of saline group.

Gender	Age	Weight	Height	BMI
F	48	65	1.65	23.88
M	17	75	1.74	24.77
M	36	67	1.68	23.74
M	25	75	1.73	25.06
M	22	67	1.72	22.68
F	35	60	1.56	24.65
M	56	65	1.68	23.03
F	36	63	1.59	24.92
F	26	62	1.62	23.62
F	40	80	1.68	28.34
M	37	59	1.72	19.94
F	16	50	1.56	20.55
F	43	45	1.52	19.48
M	26	71	1.83	21.20
M	39	62	1.63	23.34
M	33	73	1.7	25.26
M	17	63	1.71	21.55
M	24	65	1.7	22.49
M	29	57	1.7	19.72
F	25	69	1.62	26.29
F	64	40	1.44	19.29
M	19	79	1.81	24.11
F	25	83	1.58	33.25
M	19	67	1.71	22.91
F	34	69	1.52	29.86
Mean and SD	31.64 ± .24	65.24 ± .18	1.65 ± .097	23.57 ± 3.27

M = male; F = female; BMI = body mass index; SD = standard deviation

Table 4. Target dose of propofol at three time points in surgery patients

Time	Clonidine	Placebo	BIS	p
Intubation	3.923 ± 0.592	4.2 ± 0.464	40 ± 4.3	0.0697
30 min	1.5 ± 0.377	3.2 ± 0.627	45 ± 3.6	<0.0001
Awakening	0.588 ± 0.19	0.976 ± 0.268	90 ± 6	<0.0001

Table 5. Target dose of propofol at three time points in clonidine group.

Gender	OTI target	30 min target	Awakening target	BMI
M	4.0	1.3	1.3	0.3
M	3.5	2.3	2.3	0.7
M	4.0	1.8	1.8	0.6
M	3.0	1.2	1.2	0.4
M	5.0	1.5	1.5	0.5
M	5.0	2.2	2.2	1.1
M	4.0	1.2	1.2	0.4
M	3.5	2.3	2.3	0.4
M	4.0	1.5	1.5	0.6
M	4.5	1.8	1.8	0.9
F	2.0	0.4	0.4	0.2
F	4.0	1.5	1.5	0.5
F	4.5	1.6	1.6	0.6
F	3.5	1.4	1.4	0.4
F	3.6	1.5	1.5	0.6
M	4.0	1.5	1.5	0.7
F	4.5	1.4	1.4	0.6
F	4.0	1.5	1.5	0.7
F	4.0	1.5	1.5	0.6
M	3.5	1.3	1.3	0.5
F	4.0	1.3	1.3	0.6
M	4.0	1.4	1.4	0.8
F	3.9	1.4	1.4	0.6
F	4.0	1.5	1.5	0.7
M	4.0	1.4	1.4	0.8
F	4.0	1.3	1.3	0.5
Mean and SD	3.92 ± 0.59	1.5 ± 0.38	1.5 ± 0.38	0.59 ± 0.19

M = male; F = female; OTI = orotracheal intubation; SD = standard deviation

Table 6. Target dose of propofol at three time points in saline group.

Gender	OTI target	30 min target	Awakening target	BMI
F	4.0	3.4	1.65	1.2
M	4.5	3.7	1.74	1.2
M	4.0	3.4	1.68	1.3
M	4.0	3.2	1.73	0.9
M	4.0	3.5	1.72	1.0
F	3.9	3.2	1.56	0.9
M	3.7	3.0	1.68	0.7
F	4.0	3.0	1.59	0.9
F	4.0	3.0	1.62	0.9
F	4.0	3.2	1.68	0.8
M	5.0	4.0	1.72	1.0
F	4.5	3.5	1.56	1.0
F	4.5	3.5	1.52	1.0
M	4.0	3.0	1.83	0.9
M	4.9	2.8	1.63	0.7
M	4.5	4.2	1.7	1.5
M	4.0	4.0	1.71	0.8
M	5.0	3.0	1.7	0.9
M	5.0	3.8	1.7	1.3
F	4.0	1.6	1.62	0.7
F	3.0	1.4	1.44	0.3
M	4.5	3.2	1.81	0.7
F	4.0	3.0	1.58	1.4
M	4.0	3.2	1.71	1.2
F	4.0	3.2	1.52	1.2
Target dose and SD	4.2 ± 0.46	3.2±0.63	1.65 ± .097	0.97±0.27

M = male; F = female; OTI = orotracheal intubation; SD = standard deviation

difference between the groups' means of 1.7 at a confidence interval of 95% (1.44-1.99). A t value of 11.7828 with 49 degrees of freedom was found.

The two groups were similar with respect to gender, weight, height, and age. There was no significant difference in the target dose of propofol at the time of intubation: the mean value for the clonidine and placebo groups was 3.92 µg/mL and 4.2 µg/mL, respectively. Thirty minutes after the beginning of surgery, a statistically significant difference was observed: the mean target dose of propofol was 1.5 µg/mL in the clonidine groups and 3.2 µg/mL in the placebo group ($p < 0.0001$) **(Tables 5** and **6)**. A statistically significant difference was also observed at the time of awakening: the mean target dose of propofol was 0.59 µg /mL in the clonidine group and 0.98 µg/mL in the placebo group. **(Figure 1)** Target dose of propofol at intubation, 30 min and at awakening in clonidine and placebo groups **(figure 2)**.

Figure 1: Flowchart.

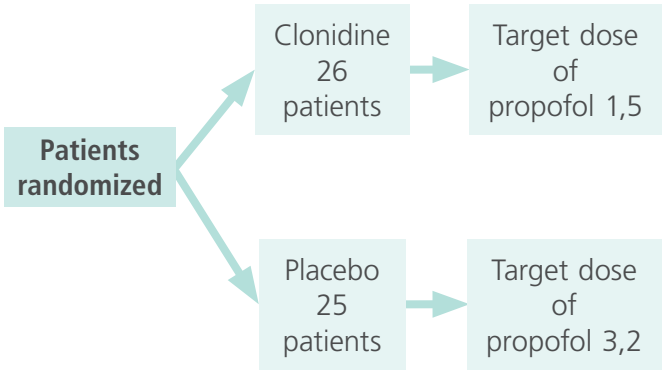
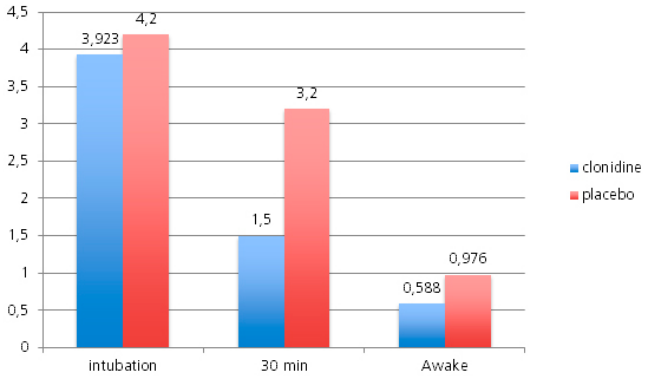


Figure 2: Target dose of propofol at intubation, 30 min and at awakening in clonidine and placebo groups.



Discussion

In this study, 16 patients undergoing laparoscopic cholecystectomy and 35 patients undergoing oral and maxillofacial surgery received total intravenous anaesthesia using propofol and remifentanil. The effect of clonidine was evaluated as a pre-medication in the target dose of propofol, during total intravenous anaesthesia with propofol and remifentanil using a target-controlled infusion pump and a modified Marsh model [30].

The effects of clonidine as a sedative, anxiolytic, analgesic, anti-emetic, in addition to the prevention of post-operative tremors [11] and maintenance of cardiovascular stability, [12, 16] are known and have been shown in various studies. Unlike other classes of sedatives, clonidine has the unique feature of causing minimal or no respiratory depression. [17]

Clonidine's analgesic effects are difficult to evaluate perioperatively, due to a lack of specific devices that can evaluate pain. However, its synergism with propofol can be shown by BIS [22, 33]. Clonidine used alone has a sedative effect, which in isolation alters the BIS values and the analgesic effect. However, it does not have sufficient hypnotic and analgesic effects to provide anaesthesia, even when administered by the intrathecal route. [25, 28, 29]

There was no difference in the target doses of propofol at the time of induction, probably because the location where clonidine's action has a sedative effect is in the *locus coeruleus*, and it is necessary to cross the blood-brain barrier to occupy its receptors and reach its maximum effect. Another study found a reduction in the induction dose of propofol, but no effect on the maintenance dose. Therefore, the infusion was based on hemodynamic variables to guide the depth of the anaesthesia, which is not ideal, especially with the use of drugs that dull the automatic response, like α_2-agonists. [14]

Various drugs have been compared with clonidine as pre-anaesthetic medications, mainly benzodiazepines such as midazolam [7] and diazepam, which show greater post-operative agitation. [10-12] Gabapentin did not show superiority in post-operative pain relief. Ketamine showed better post-operative pain relief, but also had a greater incidence of agitation and hypersalivation, [21] and magnesium sulphate showed no benefits with respect to clonidine. [22] All of the studies showed similar effects with respect to sedation level and patient satisfaction; however, only clonidine showed synergism with opioids and hypnotics [31, 32].

There are studies describing the perineural administration of clonidine to prevent chronic pain,

especially in situations where there are large nerve injuries, such as limb amputations. The probable mechanism is a decrease in production of pro-inflammatory cytokines, mainly IL1ß and TNFα. [23] Animal research has shown that clonidine administration before hypoxia improves endothelial function and modulates the inflammatory response during reperfusion. [24]

Systematic reviews performed in 2009 by the Cochrane Collaboration (revised again in 2013) concluded that α_2-agonists reduce cardiac risk, mainly in vascular surgery. Therefore, it is suggested that more studies will be necessary to confirm its benefits and safety to use in conjunction with other perioperative interventions like ß-blockers. [26]

Recently, a randomised, double-blind, multi-centre clinical trial with a sample of 10,010 patients from 135 hospitals distributed across 23 countries was performed, evaluating the effect of clonidine, placebo, and ASA status. The clonidine group received 200 µg orally 2 to 4 hours before the surgical procedure, and as a transdermal patch that released 200 µg/24 h of clonidine, which was replaced every 72 hours post-surgery. Patients were monitored for 30 days. The primary outcome evaluated was death or non-fatal myocardial infarction. This study concluded that low doses of clonidine (200 µg orally + 200 µg/24 h transdermally) did not reduce mortality or non-fatal myocardial infarction. However, it did elevate the risk of hypotension, bradycardia, and non-fatal heart attacks.

The result of this study raised questions as to the real benefits of clonidine in a perioperative scenario and the ideal dose adjustment by age group. The mean age of the patients in this study was 68.6 years. The patients were diverse, with many taking various medications, and the type of anaesthesia administered was not specified in detail in addition to the large number of co-morbid conditions in the study. However, the sample was extremely significant. [27] Similarly, there are still controversies with respect to the adequate dose in intrathecal use of clonidine, with various studies recommending doses of 15 to 450 µg. The majority suggest adjusting the dose by factors such as age, time in surgery, presence of co-morbid conditions, and the dose of local anaesthetics and opioids used. [28, 35]

Conclusions

Clonidine, administered at a dose of 3 µg/kg through intravenous infusion over 10 minutes and 10 minutes before anaesthetic induction significantly decreased the target doses of propofol at 30 min during surgery and the target dose on awakening. However, it did not reduce the doses of propofol in anaesthetic induction.

The sedative effects of clonidine act synergistically with the hypnotic effects of propofol, permitting the use of lower doses and, consequently, resulting in lower toxicity.

List of abbreviations

BIS: bispectral index
ASA: American Society Anesthesiologists
NMDA: N-*methyl*-D-aspartate
GABA: gamma-aminobutyric acid
BMI: body mass index

Competing interests

The authors declare that they no competing interests.

Authors' contributions

HMTB conceived the study and performed the statistical analyses. IMPB participed in results analysis and helped to draft the document.. LC de A participed in results analysis and helped to draft the cocument. All authors read and approved the final manuscript.

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Endnotes

1 GABA: general anesthetic receptor

2 *Locus coeruleus*: action local of the alpha2-agonist

3 BIS: hypnose monitor

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